REMARKS

I. Amendments to the Specification

The specification has been amended at page 7 to correct obvious typographical errors of mistaken references to SEQ ID NOs:3 and 4 in describing SEQ ID NO:7 (Gene 4). Particularly, " SEQ ID NO:4" in the first and last paragraphs has been replaced with "SEQ ID NO:7", and " SEQ ID NO:3" in the last paragraph has been replaced with "SEQ ID NO:5." These amendments reflect the sequences in the Sequence Listing, and, thus, no new matter has been introduced.

Table 1 on page 8 in the specification has been amended so that it no longer reflects the nucleotide numbering illustrated in Figure 1, and instead reflects the numbering illustrated in the Sequence Listing. In Figure 1A, nucleotides preceding the start codon are assigned negative numbers and the start codon is located at nucleotide number 1. However, in the Sequence Listing, as required by 37 C.F.R. §1.822 (c) no negative numbers have been assigned to the nucleotides. As a result, the start codon is located at nucleotide number 61 and the sequence terminates at nucleotide number 1234. The amendments to Table 1 reflect this numbering. Therefore, no new matter has been introduced.

II. Amendments to the Claims

Claims 21-56 and 58-103 are currently pending. Claims 38, 68, and 94 have been amended to remove the phrase "wherein % identity is determined using the Bestfit algorithm" and to recite the phrase "wherein said nucleic acid molecule encodes a polypeptide that binds FK506." These amendments are supported throughout the specification as filed, for example, on page 6, lines 20 through 28, and page 7, lines 4 through 13. No new matter has been introduced and entry is respectfully requested.

III. Rejection of claims 21-56 and 58-103 under 35 U.S.C. § 101

Claims 21-56 and 58-103 were rejected under 35 U.S.C. § 101, because the asserted utility of the claimed invention allegedly lacks a "credible, substantial, specific, or well established utility." *See* page 2, section 4 of Paper No. 28. Specifically, it is asserted that:

> [T]he instant specification fails to provide objective evidence of any activity for the encoded proteins or to show that these proteins even exist. Applicant only states that the sequence has homology to the FK506 binding protein FKBP65...There is no specific disease or specific function that is suggested by this homology; no conserved regions that would indicate that the claimed polypeptides function similarly to FKBP65 are identified."

See pages 2-3, section 4 of Paper No. 28.

Applicants respectfully disagree and traverse the rejection.

Applicants submit that the specification clearly discloses, for example, at page 6, lines 19-39, and page 7, lines 2 through 27, that the polypeptides of the invention (i.e., SEQ ID NOs: 6 and 8) share significant homology to FK506 Binding Protein 65 (also known in the art as FKBP65), which binds the macrolide FK506, which is a potent immunosuppressant (*See* page 1, line 21-22 of the specification *citing*, Schreiber *et al.* Science, 251:283-287 (1991)). This homology encompasses known regions of FK506 binding, as shown in the alignments between the claimed polypeptides (labeled as either "SEQ ID NO:8" or "SEQ ID NO:6") and the published FKBP65 (labeled as "FKBP65"), attached hereto as Exhibits A and B.

The class of immunophilins that bind FK506 and rapamycin are well-known in the art as FK506-binding proteins (FKBPs) (*See* Coss et al., J. Biol. Chem., 270(49):29336-29341 (1995) submitted herewith as Exhibit C and as cited in Applicants' IDS filed December 15, 1999 as reference C1; and page 1, lines 18-29 and page 5, lines 10-29 of the specification). As disclosed in Figure 1B in Coss et al., analysis of one member of a FKBP, the FKBP65 clone, revealed four peptidylprolyl *cis-tran*-isomerase (PPIase) signature domains. Crystallographic studies of FKBP65 have identified two regions within the PPIase domain that appear to be important for FK506 drug-binding interactions. These regions comprise five amino acid residues, Tyr, Phe, Val, Lle, and Trp, proposed to form the hydrophobic drug binding cavity and three amino acid residues Lle, Asp, and Tyr that appear to form hydrogen bonds with FK506. These seven amino acids are conserved in **all** FKBPs that have been identified to date. See Coss et al., at 29337.

The present claimed invention is no different. The claimed polypeptides possess similar PPIase Domains I, II, III, and IV of FKBP65 (see Coss et al., Figure 1 for domain locations). Additionally, each of the seven amino acids important for FK506 binding is conserved in Domains I and II of the present claimed invention (residues important for FK506 binding are indicated with asterisks "*" in Exhibits A and B, and those conserved residues are boxed).

Because the claimed proteins possess the conserved FK506-binding domains and the conserved seven amino acids important for said binding, the claimed protein can be expected to bind FK506 and therefore is a novel member of the FKBPs, as asserted on page 1, lines 13-14 and 34 of the specification. Moreover, since FK506 binding proteins are a class of well-

established and useful proteins, assignment of a new protein to a class of well-known and sufficiently conserved proteins imputes the same well-established utility to the claimed protein of the invention as is clearly taught in the specification (*See* page 5, lines 10-16 and lines 19-25).

For the reasons stated above, at least one of the utilities asserted in the specification for the Human FK506 Binding Proteins of the present invention is indeed specific, substantial and credible or well-established. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 101, for alleged lack of utility, be reconsidered and withdrawn.

IV. Rejection of claims 21-56 and 58-103 under 35 U.S.C. § 112, first paragraph

Claims 21-56 and 58-103 are also rejected under 35 U.S.C. §112, first paragraph allegedly for lack of enablement. (*See* page 3, section 5 of Paper No. 28). More particularly, the Examiner states that since the claimed invention is allegedly not supported by either a specific or well established utility, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Applicants respectfully disagree and traverse.

For the reasons discussed above in response to the rejection under 35 U.S.C. § 101, the claimed invention is supported by a well-established utility. The Examiner "should not impose a 35 U.S.C. § 112 , first paragraph, rejection grounded on 'lack of utility' basis unless a 35 U.S.C. § 101 rejection is proper." M.P.E.P. § 2107(IV) at 2100-28 (Rev. 1, Feb. 2000). Since the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection of the claims under 35 U.S.C. § 112, first paragraph, based on lack of utility of the claimed invention, should be withdrawn.

III. Rejection of claims 38-51 and 68-80 under 35 U.S.C. § 112, first paragraph

Claims 38-51 and 68-80 are also rejected under 35 U.S.C. §112, first paragraph for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner asserts that:

> [T]he claims as written encompass polynucleotides that encode proteins with 95% homology to SEQ ID NO:s 6 and 8, that vary substantially in length and also in nucleotide composition. The instant disclosure of two nucleic acids, that of SEQ ID NOs: 5 and 7, does not adequately describe the scope of the claimed genus, which encompass a substantial variety of subgenera... The specification does not provide evidence that the proteins of SEQ ID NO:6 and 8

actually exist. There is no description of the required structural and functional features of said proteins, or of the conserved regions that would be critical for these features."

See page 4, section 7 of Paper No. 28.

Applicants respectfully disagree and traverse this rejection.

The Examiner has cited *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997) (hereinafter "Eli Lilly") for the proposition that an applicant complies with the written description requirement through the use of descriptive structures common to the genus that set forth the claimed invention, or by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus. Applicants respectfully disagree that *Eli Lilly* supports a written description rejection of Applicants' claims.

The test for the written description requirement is whether one skilled in the art could reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563; 19 USPQ2d 1111, 1116 (Fed. Cir 1991); M.P.E.P. § 2163.02.

According to the court in *Eli Lilly*, a written description may be adequate if it defines "a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Eli Lilly*, 119 F.3d at 1569. In *Eli Lilly* however, the genus was described entirely by function, with no reference at all to structure. The presently claimed genus, in contrast, is entirely described by structure (e.g., disclosure of SEQ ID NOs:6 and 8).

The specification as filed contains a detailed description of the claimed nucleotide (SEQ ID NOs:5 and 7) and polypeptide sequence (SEQ ID NOs:6 and 8). The structural recitation of SEQ ID NOs:6 and 8 constitutes a recitation of a structural feature common to all the members of the claimed genera, which features "constitute a substantial portion of the genus." *Id.* That is, the recitation of the polypeptide sequence of SEQ ID NOs:6 and 8, is a recitation of the structural feature common to the members of the claimed genera because polypeptide sequences that are at least 95% homologous to the polypeptide sequence of SEQ ID NOs:6 or 8 will share at least some structural features common to the members of the specified genera because the polypeptides included within the genera will have 95% of their polypeptide sequences (primary structure) in common with the polypeptide sequence of SEQ ID NOs:6 or 8.

Further, page 12, lines 1-13, and page 13, line 1 to page 14, line 14 of the specification describes to one of skill in the art how to readily envision those polypeptides which would be at least 95% identical to the full-length protein. This is merely a simple exercise of inserting, deleting or substituting up to 5% of the amino acid residues in the subject sequence (see page 13, lines 5-7 of the specification).

Further, as discussed in the utility section above, the various conserved domains and conserved FK506 drug-binding amino acids were well-known in the art at the time the earliest priority application was filed. Thus, an examination of SEQ ID NOs:6 and 8 would reveal those conserved domains present in the claimed protein (as shown in Exhibits A and B). Therefore, one of skill in the art could readily envision which 5% of amino acid residues could be mutated without a loss of function. For instance, one of skill in the art could test these variants using, for example, the PPIase activity assay described by Galat et al, (*See* page 5, lines 26-29 of the specification) among other assays, to determine whether these polypeptide variants retained the function of the polypeptides having the amino acid sequence of SEQ ID NOs:6 or 8.

Nonetheless, Applicants point out that claims 38, 68, and 94 have been amended to recite "wherein said nucleic acid molecule encodes a polypeptide that binds FK506." Applicants reserve the right to prosecute the subject matter of the unamended claims in future continuing applications.

Based upon the comments above, one of skill in that art could readily envision the identity of the members of the claimed genera based upon the teachings of the specification as filed, and thus could reasonably conclude that the inventors had possession of the claimed invention in the specification as filed. Accordingly, Applicants respectfully request that the rejection to these claims be reconsidered and withdrawn.

Claims 38-51 and 68-80 are also rejected under 35 U.S.C. §112, first paragraph for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Applicants have previously traversed this rejection, on the grounds that since the disclosed or otherwise known methods of making and screening the claimed polypetides may be used to determine without undue experimentation, whether a given polypeptide or variant thereof encompassed by the claims exhibits, for example, PPIase activity, the enablement requirement is fully satisfied. The Examiner responds:

> [T]he instant specification discloses insufficient guidance that the polypeptides of SEQ ID NOs: 6 or 8, or variants thereof, exhibit PPIase activity, or any other activity for that matter...the examiner contends that the function of the polypeptides of SEQ ID NOs:6 and 8, or variants thereof, is unpredicatable based on less that 50% homology with FKBP65..."

Preliminarily, Applicants reiterate that claims 38, 68, and 94 have been amended to recite "wherein said nucleic acid molecule encodes a polypeptide that binds FK506."

As noted above, the polynucleotides of the instant invention encode polypeptides which share significant homology to FKBP65, which binds the macrolide FK506. This homology encompasses known FK506-binding protein PPIase signature domains, as shown in the alignments between the claimed polypeptides (labeled as either "SEQ ID NO:8" or "SEQ ID NO:6") and the published FKBP65 (labeled as "FKBP65"), attached hereto as Exhibits A and B. The polypeptides of the instant invention, therefore, can exhibit the same FK506-binding and PPIase activity as FKBP65. Also, as discussed above, one of skill in the art could readily test the claimed invention using, for example, the PPIase activity assay described by Galat et al. (*See* p. 5, lines 26-29 of the specification) to determine whether these polypeptide variants retained the function of the polypeptides having the amino acid sequence of SEQ ID NOs:6 or 8.

Therefore, Applicants contend that since the disclosed or otherwise known methods of making and screening the claimed polypeptides may be used to determine without undue experimentation, whether a given polypeptide or variant thereof encompassed by the claims exhibits, for example, PPIase activity, the enablement requirement is fully satisfied. Accordingly, Applicants respectfully request that the rejection to these claims be reconsidered and withdrawn.

Conclusion

Applicants respectfully request that the remarks above be entered and made of record in the file history of the instant application. Applicants believe that all objections and rejections have been obviated or overcome and the claims are in condition for allowance.

If there are any fees due in connection with the filing of this paper, please charge such fees to Deposit Account No. 08-3425.

Respectfully submitted,

Dated: April 29, 2002

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EXHIBIT A

FKBP65 vs. SEQ ID NO:6

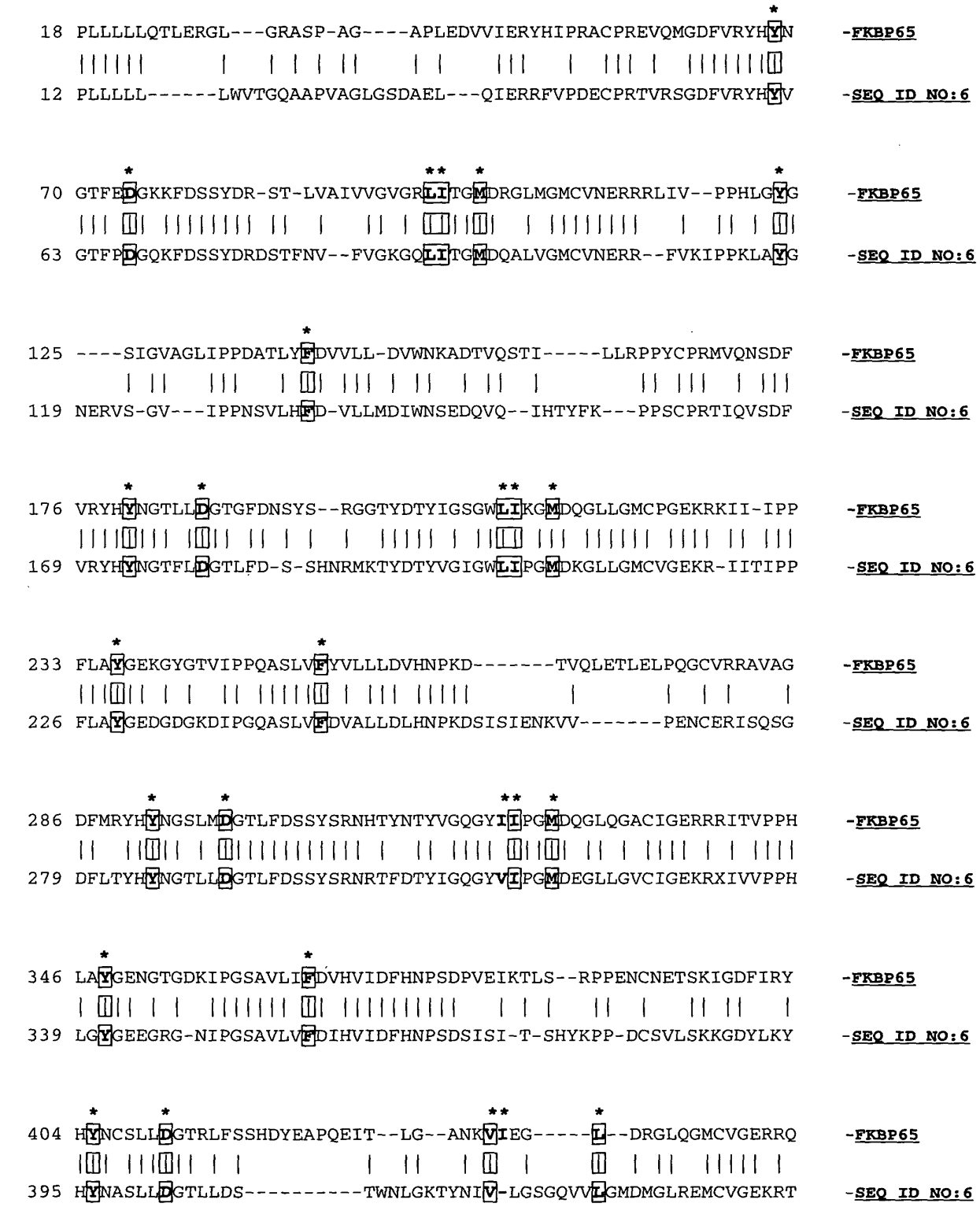
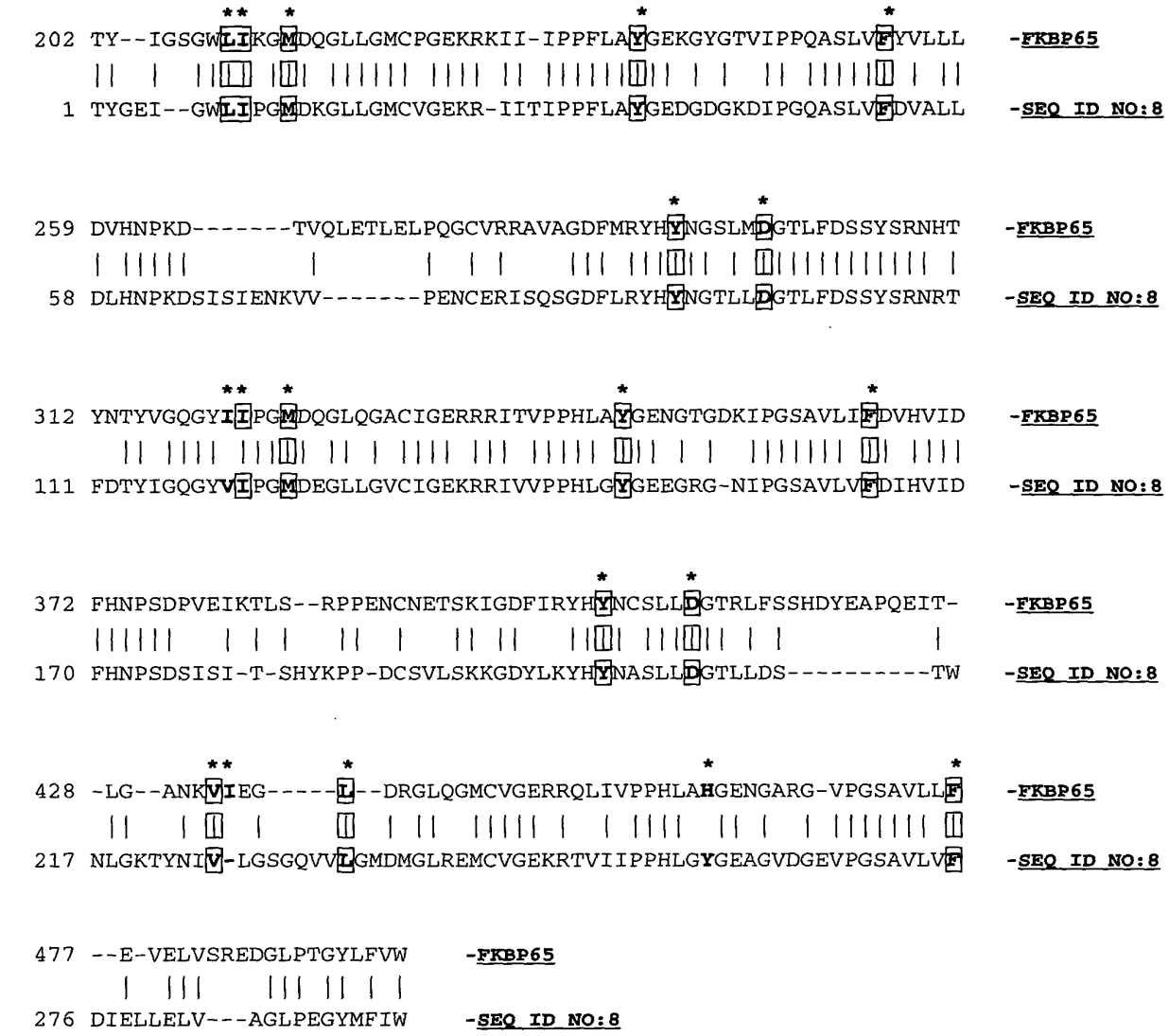
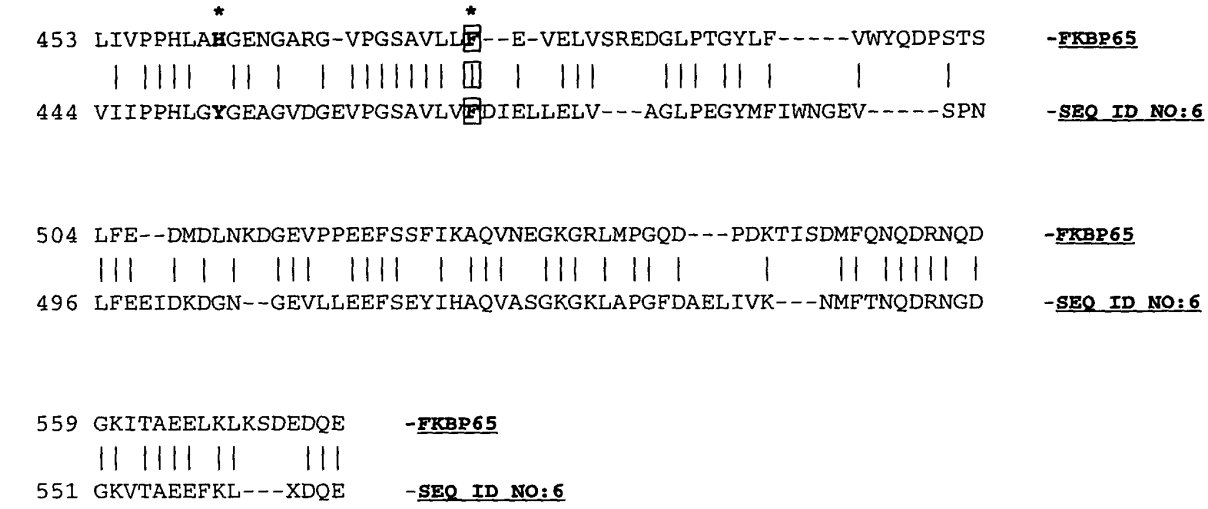


EXHIBIT B

FKBP65 vs. Seq ID No.8





FKBP65 Domain I = residues 61 to 147
Domain II = residues 173 to 259
Domain III = residues 285 to 371
Domain IV = residues 398 to 483

Docket No.: PF392
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Ruben et al.

Application No.: 09/225,502 Group Art Unit: 1644

Filed: January 6, 1999 Examiner: A. Decloux

For: Human FK506 Binding Proteins

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Page 7, paragraph beginning at line 3:

SEQ ID NO:~~4~~ 7 shows the nucleic acid sequence of a cDNA which is a splice variant of the gene described as SEQ ID NO:5. The translation product of this gene (SEQ ID NO:8) also shows very strong homology to FK506 Binding Protein 65 ("FKBP65"). See Coss M.C. et al., J. Bio. Chem., (1995) 270:29336.

Page 7, paragraph beginning at line 25:

A full-length cDNA clone, and corresponding protein, may be produced by those of ordinary skill in the art by aligning SEQ ID NO:~~3~~ 5 and SEQ ID NO:~~4~~ 7. Since these clones are nearly identical until they diverge at the 3'end, the 5' portion of SEQ ID NO:~~4~~ 7 may be supplied by using the coding region from SEQ ID NO:~~3~~ 5.

In the Claims

38. (Once amended) An isolated nucleic acid molecule encoding a first amino acid sequence at least 95% identical to the entire length of a second amino acid sequence selected from the group consisting of:

(a) an amino acid sequence encoding amino acid residues 1 to 574 or SEQ ID NO:6;

(b) a nucleotide sequence encoding amino acid residues 2 to 574 of SEQ ID NO:6;

(c) an amino acid sequence encoding amino acid residues 25 to 574 of SEQ ID NO:6; and

(d) an amino acid sequence encoding amino acid residues 1 to 388 of SEQ ID NO:8;

~~wherein % identity is determined using the Bestfit algorithm.~~ wherein said nucleic acid molecule encodes a polypeptide that binds FK506.

68. (Twice amended) An isolated nucleic acid molecule encoding a first amino acid sequence at least 95% identical to the entire length of a second amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of the full-length polypeptide encoded by the cDNA contained in clone HSYBM46 as deposited with the ATCC as accession number 209193,

(b) the amino acid sequence of the full-length polypeptide, lacking the N-terminal methionine, which is encoded by the cDNA contained in clone HSYBM46 as deposited with the ATCC as accession number 209193,

(c) the amino acid sequence of the secreted portion of the polypeptide encoded by the cDNA contained in clone HSYBM46 deposited with the ATCC as accession number 209193;

~~wherein % identity is determined using the Bestfit algorithm.~~ wherein said nucleic acid molecule encodes a polypeptide that binds FK506.

94. (Twice amended) An isolated nucleic acid molecule encoding a first amino acid sequence at least 95% identical to the entire length of an amino acid sequence of the polypeptide encoded by the cDNA contained in clone HFKBC47 as deposited with the ATCC as accession number 209193; ~~wherein % identity is determined using the Bestfit algorithm.~~ wherein said nucleic acid molecule encodes a polypeptide that binds FK506.

TABLE 1. FEATURES OF PARTICULAR SECRETED PROTEINS

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	NOTE	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HMEAA94	209193 08/01/97	pBS SK-	1	1234	~~60~~ **1**	~~1174~~ **1234**		~~1~~ **61**	1	2	1	26	27	336
2	HL1AP03	209193 08/01/97	pBS SK-	3	2145	1	2145		2		4			1	441
3	HSYBM46	209193 08/01/97	pCMVSport 3.0	5	3391	1	3391		130	130	6	1	24	25	574
4	HFKBC47	209193 08/01/97	pBS SK-	7	1251	1	1251		3		8			1	388